

## **REMARKS**

In view of the following remarks, the Applicant respectfully requests allowance of Claims 1-4, 6-16, and 26-30, the only claims pending and under consideration in this application.

### ***Formal Matters***

Claims 1 and 26 have been amended for clarity as requested by the Examiner.

Claim 13 has been amended to be consistent with the amendments to Claim 1.

Because these amendments add no new matter, entry thereof by the Examiner is respectfully requested.

### ***Claim Rejections – 35 USC § 112***

The Examiner rejects Claims 1-4, 6-16 and 26-30 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner asserts that Claim 1 is unclear because in reciting "identifying... candidate probe sequences" in step (a) and "providing an array of candidate nucleic acid probes immobilized on a surface" in step (b), it is unclear if these are intended to be the same or different candidate sequences.

In response, the Applicants have deleted the first recitation of the term "candidate" in step (i).

The Examiner asserts that Claims 1 and 26 are unclear because in using passive language (i.e. to produce in step (ii) of Claim 1 and step (c) of Claims 1 and 26) it is unclear whether applicant intends for this to be an active method step (i.e. producing), an intended use, or a further limitation of the claimed method.

In response, the Applicants have amended step (ii) of Claim 1 to remove the passive "to produce" language and have added an active "producing" step (iii). The Applicants have also amended step (c) of Claims 1 and 26 to remove the passive "to produce" language and to revise step (c) to be an active "clustering" step rather than an "evaluating" step.

The Examiner asserts that Claims 1 and 26 are unclear because in using passive language (i.e. to identify in step (d) of both claims) it is unclear whether applicant intends for this to be an active method step (i.e. identifying), an intended use, or a further limitation of the claimed method.

In response, the Applicants have amended Claims 1 and 26 to remove the passive "to identify" language and to revise step (d) to be an active "identifying" step rather than an "evaluating" step.

The Examiner asserts that it is unclear in what way the claimed method of Claim 1 achieves the purpose of its preamble because Claim 1 is directed to methods for "identifying a sequence of a nucleic acid" but results in a step of "evaluating any remaining candidate probe sequences not among said clustered probe sequences."

As noted above, the Applicants have amended step (d) of Claims 1 and 26 to be an active "identifying" step, which is now consistent with the preamble of these claims.

Claim 13 has been amended to be consistent with the amendments to Claim 1.

In view of the amendments and discussion above, the Applicants submit that Claims 1-4, 6-16 and 26-30 clear and definite and respectfully request withdrawal of this rejection.

### ***Claim Rejections - 35 USC § 103***

The Examiner has rejected Claims 1, 2, 6-10 and 26-30 under 35 U.S.C. § 103(a) as being obvious over Li et al. (Bioinformatics, 2001, v. 17 p.1067; "Li") in view of Ben-dor et al. (J. Comp. Biol., v. 6 p. 281; "Ben-dor").

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. Exemplary citations include:

- *Pharmastem Therapeutics v. Viacell et al.*, 2007 U.S. App. LEXIS 16245 (Fed. Cir. 2007) which states: "the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a

reasonable expectation of success in doing so," (*citing KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007));

- *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007) which states: "[t]he Supreme Court recently explained that 'a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,'" (*citing KSR Int'l Co.* at 1741); and
- *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006) which states "[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references,'" (*citing In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004)).

The claimed invention is drawn to methods of identifying a sequence of a nucleic acid that is suitable for use as a substrate surface immobilized normalization probe. The claimed methods include an empirical evaluation step in which candidate probes (having candidate probe sequences) are immobilized on a substrate in an array format, subjected to different experimental conditions to produce empirical data values (see step (b) of claims 1 and 26). These empirical data values are then employed to cluster the candidate probe sequences into groups and identify suitable normalization probes.

In making this rejection, the Examiner asserts that Li et al. teach a computer-implemented method and program for selecting an optimal number of DNA oligonucleotides for gene expression arrays, including the empirical evaluation step as described above. The Examiner asserts that the selection criteria directed to frequency calculation and the free energy calculation in Li are both teachings for empirical evaluation as in Claims 1 and 26. The Examiner goes on to assert that Li's candidate probe evaluation for three different model organisms equates to experimental conditions as claimed. The Examiner also asserts that Li teaches subjecting arrays to experimental conditions for producing gene expression data.

The Examiner notes that Li does not specifically teach limitations directed to

evaluating gene expression data based on clustering.

To remedy this deficiency, the Examiner cites Ben-dor, stating that it would have been obvious to someone of ordinary skill in the art to practice the array probe selection method of Li using the clustering method of Ben-dor to rapidly analyze gene expression data produced by candidate probes in order to provide additional information for selecting optimal probes.

In response, the Applicants submit that Li fails to teach employing any empirical data in the probe selection process describe therein. The Examiner is directed to page 1069, right column, under the heading "Algorithm", which provides an overview of the probe selection methods of Li, the entirety of which is reproduced below for convenience:

#### **ALGORITHM**

ProbeSelect is written in C++ and was developed on Sun workstations running Solaris. The code is portable for linux and has also been implemented on HP workstations. The program consists of seven major components, described in detail below: (1) make a suffix array of the coding sequences from a whole genome; (2) build a sequence landscape for every gene based on the sequence suffix array; (3) choose probe candidates based on sequence features and the sequence word rank values; (4) search for matching sequences in the whole genome, allowing a certain number of mismatches by the program *myersgrep* (Myers, 1998); (5) locate match sequence positions in all genes; (6) calculate the free energy ( $\Delta G$ ) and melting temperature ( $T_m$ ) for each valid target sequence; (7) select match sequences that have stable hybridization structures with a probe based on free energy data and allow good discrimination with other targets in the genome. The architecture of the program is shown in Figure 2.

As is clear from this excerpt, Li does not include analysis of empirical data in the probe selection method disclosed therein, let alone one which employs array-based empirical data of candidate probes sequences as is claimed. In fact, there is no empirical data shown in Li: all of their probe selection steps are conducted *in silico* without taking into account any empirical data whatsoever. The "empirical data" referred to by the Examiner (i.e., frequency calculation, free energy calculation and candidate probes designed for three different model organisms) were all done solely *in*

*silico* in the absence of an empirical evaluation step that includes producing data from actual array-based experiments.

Ben-dor is cited by the Examiner for its asserted teaching of clustering algorithms. However, the Applicants submit that this reference fails to remedy the fundamental deficiency in Li, i.e., employing empirical data in probe sequence identification as is claimed.

Moreover, the Applicants submit that neither Li nor Ben-dor suggest employing empirical data in probe sequence identification as is claimed. First, Ben-dor is not drawn to probe selection at all, but rather to clustering gene expression patterns obtained from array experiments. As such, this reference fails to suggest using empirical data in probe sequence identification as claimed. Second, Li includes no empirical data in their probe selection methods and specifically state that "[w]e have developed an heuristic approach that is efficiently computable at all levels and should provide a good approximation to the true optimum set" (see abstract). Applicants submit that Li's characterization that the method disclosed therein is "a good approximation to the true optimum set" makes clear that no empirical evaluation as claimed in Li is taught or even suggested.

Therefore, because the combined teachings of Li and Ben-dor fail to teach or suggest each and every limitation of the claims, a *prima facie* case of obviousness has not been established. Withdrawal of this rejection is thus respectfully requested.

The Examiner has rejected Claims 1-4, 7-9, 13-16 and 26-30 under 35 U.S.C. § 103(a) as being obvious over Sung et al. (Proc. of Computational Systems Bioinformatics (CSB'03) August 11-14 2003, p. 1-10; "Sung") in view of Ben-dor et al. (J. Comp. Biol., v. 6 p. 281; "Ben-dor").

Similar to the rejection above, the Examiner asserts that Sung's disclosed method of probe selection includes all elements of the claimed methods except the limitations directed to evaluating gene expression using a clustering algorithm. To remedy this deficiency, the Examiner again cites Ben-dor.

In making this rejection, the Examiner asserts that Sung teaches empirically evaluating an array of candidate probes under and subjected to different experimental

conditions as is claimed, citing Tables 2 and 5.

However, the Applicants submit that Sung provides no such teaching. Specifically, Tables 2 and 5 of Sung do not show any array assay data, nor its use in identifying candidate probe sequences as is claimed. Rather, these tables show certain parameters of their design/selection algorithm as well as classification of the probes returned (e.g., Time for Homogeneity and Sensitivity Criteria Filtering, Number of Genes with Probes, etc.). Therefore, the Applicants submit that Sung fails to teach the empirical evaluation step as is claimed.

Moreover, Sung et al. fail to suggest using empirical data in their probe selection algorithm. Throughout Sung, each and every probe design and selection step is decidedly performed *in silico*, without any empirical data value input. Indeed, on the fourth page of Sung, top of left column, the entirety of the algorithm is outlined as follows:

1. Filter oligo probes in the genome which fail to satisfy homogeneity criterion.
2. Filter oligo probes in the genome which fail to satisfy sensitivity criterion.
3. Filter oligo probes based on the specificity criterion using the Pigeon-Hole Principle. This is to remove probes that can cross-hybridize with any of the sub-sequences in the whole genome.

As is clear from the above (and similar to Li), Sung provides not a single empirical array-based experiment using a probe designed/selected using their algorithm. As such, the Applicants submit that Sung simply cannot teach or suggest empirical evaluation in a candidate probe sequence identification method as is claimed.

As argued above, the Applicants submit that Ben-dor fails to teach employing empirical data in probe sequence identification as is claimed, and therefore fails remedy the fundamental deficiency in Sung. Indeed, Ben-dor is not drawn to probe selection at all, but rather to clustering gene expression patterns from array data.

Therefore, because the combined teachings of Sung and Ben-dor fail to teach or suggest each and every limitation of the claims, a *prima facie* case of obviousness has not been established. Withdrawal of this rejection is thus respectfully requested.

The Examiner has rejected Claims 10 and 11 under 35 U.S.C. § 103(a) as being obvious over Li et al. (Bioinformatics, 2001, v. 17 p.1067; "Li") in view of Ben-dor et al. (J. Comp. Biol., v. 6 p. 281; "Ben-dor") as applied to Claims 1, 2, 6-10, 12-16 and 26-30, above, and further in view of Cao et al. (Cross Comparison of DNA Microarray Platforms, Alliance for Cellular Signaling Laboratories, Sept. 26, 2003, p. 1-23; "Cao").

In making this rejection, the Examiner re-asserts that Li and Ben-dor make obvious a method for selecting an optimal number of probes for use in gene expression arrays, as set forth above and applied to claims 1, 2, 6-10, 12-16 and 26-30.

The Examiner then states that while Li and Ben-dor do not specifically teach log-ratio limitation as in claims 10 and 11, Ben-dor clearly teach and suggest the calculation of log-ratios of intensities.

To remedy this deficiency, the Examiner asserts that Cao et al. teach calculation of log-ratio values across a number of different experimental conditions and values in the range of -0.16 to 0.44 as in claims 10 and 11.

However, as argued above, the Applicants submit that the combined teachings of Li and Ben-dor fail to teach employing empirical data in the identification of probe sequences as is claimed. As Cao is cited merely for its teaching of log-ratio values, this reference fails to remedy this fundamental deficiency in the teachings of Li and Ben-dor.

Therefore, because the combined teachings of Li, Ben-dor and Cao fail to teach or suggest each and every limitation of the claims, a *prima facie* case of obviousness has not been established. Withdrawal of this rejection is thus respectfully requested.

### ***Provisional Obviousness-Type Double Patenting***

The Examiner has provisionally rejected Claims 1-4, 6-16 and 26-30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 10/871,303.

The Applicants respectfully request that this rejection be held in abeyance until allowance of claims in the subject application.

**CONCLUSION**

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone John Brady at (408) 553-3584.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10030468-1.

Respectfully submitted,

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